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Deciphering DNA-Based Asymmetric Catalysis through Intramolecular Friedel–Crafts Alkylations

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We describe asymmetric intramolecular Friedel–Crafts alkylations with a DNA-based hybrid catalyst and propose a plausible binding model. This study shows promise for studying relationships between the helical chirality of DNA and enantioselectivity of the chemical reaction.

The application of DNA-based hybrid catalysts for enantioselective synthesis emerged only a few years ago. In 2005, Feringa and Roelfes introduced the concept of a novel catalyst on the basis of supramolecular assembly using a copper complex of a nonchiral ligand that can bind to DNA.[1] Since then, DNA-based hybrid catalysts have been successfully applied to various asymmetric carbon–carbon or carbon–heteroatom bond-forming reactions such as the Diels–Alder reaction, Michael addition, and Friedel–Crafts reactions.[2] The use of DNA in these Lewis acid catalyzed reactions led to high enatioselectivity, whereas the corresponding products were obtained as racemates in the absence of DNA. Therefore, it is clear that the enantioselectivity of the reactions originated from DNA; however, the stereoinduction mechanism has been much less studied to date.[3, 4] This aroused our curiosity as to how DNA induces enantioselectivity in the reactions. To investigate the stereoinduction mechanism of DNA-based asymmetric synthesis, we thought that an intramolecular reaction system might be more suitable because it significantly reduces the conformational freedom compared with an intermolecular reaction. Of the reported intermolecular reactions, we selected the Friedel–Crafts reaction as a model reaction for the intramolecular reaction.[5] The previously reported intramolecular cyclization reaction of **1** by bis(oxazolinyl)pyridine-scandium(III) triflate complexes can be considered as a good candidate for our investigation. [7b] Herein, we report asymmetric intramolecular Friedel–Crafts alkylations with a DNA-based hybrid catalyst and propose a plausible stereochemical model to explain the obtained enantioselective outcome.[6, 7]

We first investigated the reaction of **1** with DNA-based catalysts consisting of st-DNA-bound copper(II) complexes with the 4,4′-dimethyl-2,2′-bipyridine (dmbpy) ligand, which gave the best result for intermolecular reactions performed in water at 5 °C for two days. It was found that the combination of st-DNA and Cu(dmbpy) provided cyclized product **2** in 18% yield with 35% enantiomeric excess (ee) (Figure 1).[2g] The absence of st-DNA resulted in the corresponding product as racemates (see SI).

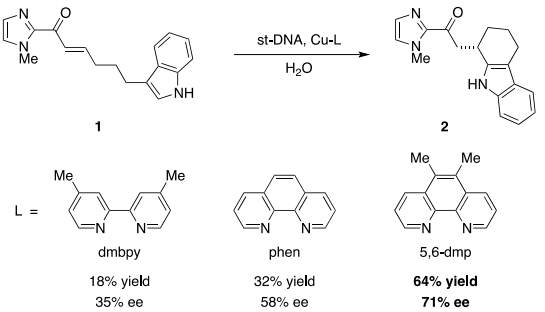


Figure 1. DNA-based intramolecular Friedel–Craft alkylation

The absolute configuration of the product was determined by HPLC analysis by comparison with the previous report.[7b] In the present reaction system, it was found that the (*S*)-enantiomer is obtained as the major enantiomer. To improve the reaction, the various ligands were examined (see SI, Figure S1 and Table S1). The catalysts based on the phenanthroline ligands improved enantioselectivity to 58% ee. The best ee value was obtained with a phenanthroline derivative, namely 5,6-dimethyl-1,10-phenanthroline (5,6-dmp), up to 71% ee (for the (*S*)-enantiomer). All further experiments were performed using the copper complex of 5,6-dmp selected as the optimized catalytic system.

To construct a molecular model of the DNA-mediated enantioselective reaction, the effect of the DNA sequence on this catalysis was investigated using synthetic oligonucleotides; the results are summarized in Table 1. Oligonucleotides with sequences $d(TCAGGGCCCTGA)_2$, reported to afford high enantioselectivity for an intermolecular Friedel–Crafts reaction, resulted in lower ee values (50%) than st-DNA in the present reaction system.[2g] GC-rich duplexes gave rise to a slight decrease in enantioselectivity (60%), whereas the presence of TA-rich duplexes was beneficial to this reaction. These results indicate that the sequence selectivity of the catalytic reaction differs from that of the intermolecular system. In the present reaction system, oligonucleotides with sequences $d(TGTGTGCACACA)_2$ induced the highest ee (up to 77% ee; Table 1, entry 6). As shown in entry 7, while duplex DNA consisting of d(GTGTGTGTGTGT) and

d(CACACACACACA) gave the product with 74% ee, each single-stranded DNA sequence resulted in an almost racemic product (Table 1, entries 8 and 9). When the length of the oligonucleotides was reduced from a dodecamer to an octamer, the ee value dropped, and the product was obtained as racemates using a tetramer (Table 1, entries 10 and 11). Increasing the DNA length above that of the dodecamer did not lead to further improvement in the enantioselectivity (Table 1, entries 12). In regard to chirality of the DNA double helix, Z-DNA with a left-handed double helical structure was used as a chiral scaffold. Z-DNA gave rise to a decrease in enantioselectivity for the present system, contrary to our expectation that left-handed Z-DNA could primarily induce the opposite enantiomer compared with right-handed B-DNA (Table 1, entry 13). In addition to the duplex, two G-quadruplex-forming sequences (h-telo and c-myc) were investigated and gave the desired product, albeit with low enantioselectivity (Table 1, entries 14 and 15).[8]

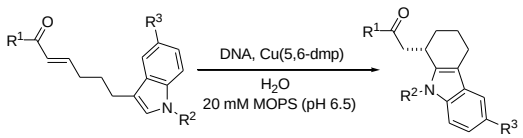
Table 1. Dependence of the ee on the DNA sequence in the case of Cu-(5,6-dmp)

entry	DNA sequence	ee (%)[a]
1	st-DNA	71
2	$d(CGCGCGCGCGCG)_2$	60
3	$d(TCAGGGCCCTGA)_2$	50
4	$d(AAAAAATTTTTT)_2$	60
5	$d(TATATATATATA)_2$	74
6	$d(TGTGTGCACACA)_2$	77
7	d(GTGTGTGTGTGT) + d(ACACACACACAC)	74
8	d(GTGTGTGTGTGT)	2
9	d(ACACACACACAC)	3
10	$d(TGCA)_2$	0
11	$d(TGTGCACA)_2$	50
12	$d(TGTGTGTGTGTGCACACACACACA)_2$	77
13[b]	$d(C^{Me}GCGC^{Me}GCGC^{Me}GCG)_2$	40
14[c]	h-telo d(AGGGTTAGGGTTAGGGTTAGGG)	19
15[c]	c-myc d(AGGGAGGGCGCTGGGAGGAGGG)	26

[a] All experiments were carried out with 1.1 □M of substrates, 1.4 mg/mL DNA, 30 mol% Cu-ligand, at 5 °C, in 20 mM MOPS buffer (pH 6.5), for 1 day, unless otherwise noted. [b] Experiments were carried out with 50 mM NaCl, ^{Me}G = 8-methylguanine [c] Experiments were carried out with 100 mM KCl.

The scope of this intramolecular system was investigated under optimized reaction conditions (Table 2). The inability to form a chelate with copper did not perform the present catalysis (Table 2, entry 1).[9] In place of 2-acyl imidazole, use of the 2-acyl pyridyl group decreased enantioselectivity of the product (Table 2, entry 2). Tethered indole derivatives containing electron-withdrawing or electron-donating substituents catalyzed by st-DNA/Cu(5,6-dmp) gave the corresponding product in moderate yield with good enantioselectivity (Table 2, entries 3–6). The obtained ee values indicate that the substituents on indole do not have a significant influence on enantioselectivity. Although the *N*-methyl indole afforded the corresponding product with high ee in the intermolecular system, the tethered *N*-alkylated indole substrates gave products with very low enantioselectivities in this intramolecular system (Table 2, entries 7 and 8).[2g] Unfortunately, we observed that the corresponding reaction to form the five-membered ring was unsuccessful.[7b]

Table 2. Substrate scope



entry	R^1	R^2	R^3	yield (%)[a] st-DNA	ee (%)[a] st-DNA	ee (%)[b] DNA-1
1	ph	H	H	no conversion	nd	nd
2	py	H	H	54	38	nd
3	Im	H	H	64	71	77
4[c]	Im	H	F	41	70	70
5[d]	Im	H	Br	51	77	80
6[e]	Im	H	MeO	45	78	82
7	Im	Me	H	91	7	nd
8	Im	Bn	H	12	4	nd

[a] Experiments were carried out with 0.045 mM of substrates, 1.4 mg/mL st-DNA, 30 mol% Cu-ligand, at 5 °C, in 20 mM MOPS buffer (pH 6.5), for 1 day, unless otherwise mentioned. [b] DNA-1: $d(TGTGTGCACACA)_2$, 1.1 □M of substrates, 1.4 mg/mL st-DNA, 30 mol% Cu-ligand, at 5 °C, in 20 mM MOPS buffer (pH 6.5), for 1 day. [c] reaction time: 12 h. [d] reaction time: 18 h. [e] reaction time: 8 h. nd: no experiment was performed and no datum is available.

Based on these data we constructed a tentative binding model, which will allow us to decipher the DNA-based asymmetric catalysis. The oligonucleotides with sequences $d(TGTGTGCACACA)_2$, which afforded the best enantioselectivity for the present reaction to date, were selected as receptors for the copper(II) complexes. In regard to the binding mode to DNA, the melting temperature of $d(TGTGTGCACACA)_2$ slightly increased in the presence of Cu(5,6-dmp), suggesting that the DNA duplex is stabilized by binding to Cu(5,6-dmp).[10] Furthermore, viscosity studies of st-DNA solution with Cu(5,6-dmp) gave the results to support the intercalative binding. Because it is also known that planar heterocyclic aromatic rings such as phenanthroline or acridine insert between the base pairs of the DNA double helix through intercalative binding,[11] we postulate that Cu(5,6-dmp) complexes insert into the base-pair layers in the DNA minor groove by intercalation. Subsequently, the binding model was constructed based on (*S*)-enantiomer complex with Cu(5,6-dmp) (Figure 4). These models are tentative and we are currently undertaking computational studies to explain stereoinduction mechanism.

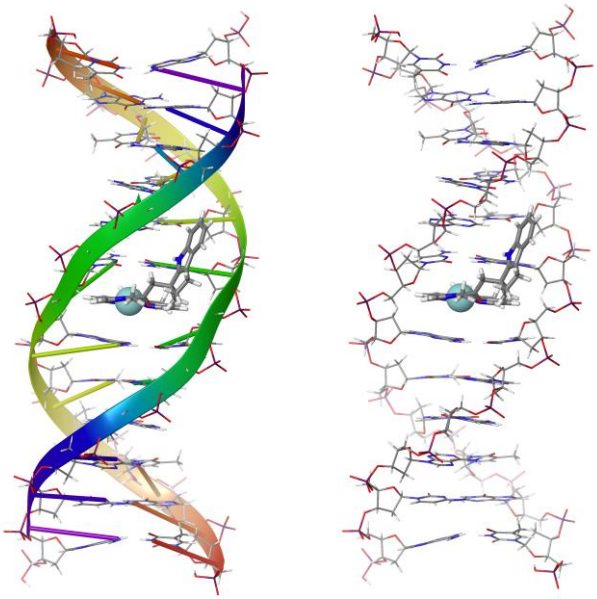


Figure 4. Tentative binding model of DNA and (*S*)-enantiomer complex with Cu(5,6-dmp) based on the intercalation.

Conclusions

In this study, we describe asymmetric intramolecular Friedel–Crafts alkylations with a DNA-based hybrid catalyst and propose a plausible binding model on the basis of the inference from the data. Although further investigation is needed to understand the binding mode of the copper complex to DNA, our model shows promise for studying relationships between the helical chirality of DNA and enantioselectivity of the chemical reaction. Further studies are under way to explore more details of the present catalysis, including mechanistic studies as well as the improvement of enantioselectivity.

Notes and references

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